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WORLD INTELLECTUAL PROPERTY ORGANIZATION

International Office

INTERNATIONAL APPLICATION, PUBLISHED IN ACCORDANCE WITH THE INTERNATIONAL PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification[6]:

A61K 31/00 A2

(11) International Publication Number: WO 99/52514

(43) International Publication Date: 21 October, 1999 (10-21-99)

(21) International Reference Number: PCT/AT99/00093

(22) International Application Date: 14 April 1999 (04-14-99)

(30) Priority Dates:

A 636/98 14 April, 1998 (04-14-98) AT

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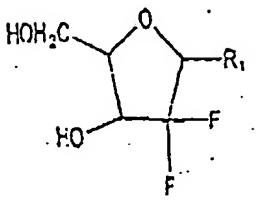
(81) Countries of Designation: AL, AU, BR, CA, CN, CZ, HU, ID, IL IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, TR, UA, US, VN, YU, ZA, Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

*Without international search report; will be republished upon receipt of report.*

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract [English in original]



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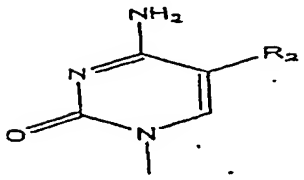

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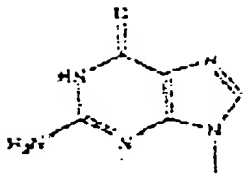

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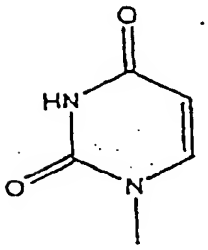

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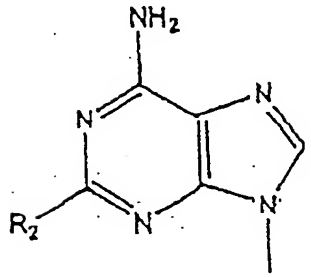

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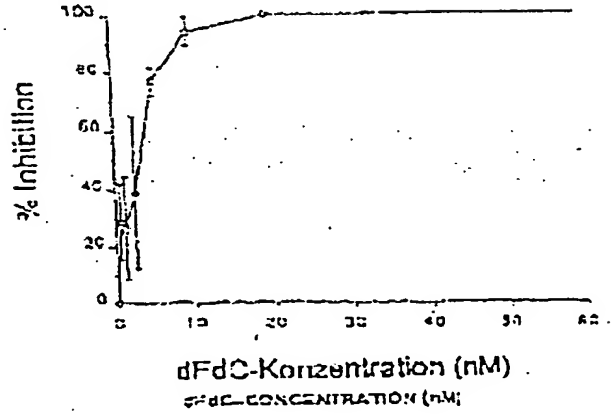


dFdC Concentration (nM)

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# PHARMACEUTICAL COMPOSITION

## BACKGROUND OF THE INVENTION

### Scope of the Invention

The present invention relates to the field of pharmaceutical treatment, and proposes the novel use of 2',2'-difluoronucleosides in the production of compositions for use in immunosuppressive therapy, and new pharmaceutical compositions and products for use in treating humans and animals.

### Prior Art

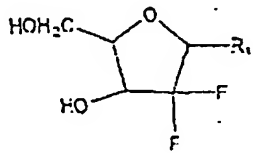
Suppressing the reactivity of the immune system using immunosuppressive therapy is of great medical importance in preventing the rejection of allogenic transplants in transplant patients, and in the treatment of autoimmune illnesses. In recent years a limited number of new pharmaceuticals designed for use in immunosuppressive therapy, such as Cyclosporin A., Tacrolimus, Mycophenolate Mofetil, Daclizumab, and Rapamycin, have been developed.

There continues to be an urgent need for the development of more effective and better-tolerated methods for treating autoimmune illnesses, and for preventing the rejection of allogenic transplants in transplant patients. The present invention thus focuses on preparing new pharmaceutical compositions and products for use in this field of therapy.

It has been shown that 2',2'-difluoronucleosides produce antiviral effects in vitro (US-Patent 4,808,614) and oncolytic activity in standard cancer screening tests (US Patent 5,464,826). Of these compounds, the 2'-desoxy-2',2'-difluorocytidine (Gemcitabine, dFdC) has been researched extensively in terms of its oncolytic activity (Kaye, *J. Clin. Oncol.* 12, 1527 (1994)). Based upon the results of these studies, Gemcitabine hydrochloride has received official approval for use in treating non-parvicellular bronchial carcinomas and/or pancreatic carcinomas in more than 50 countries. Further studies into the treatment of breast, bladder, and ovarian carcinomas with Gemcitabine are currently underway.

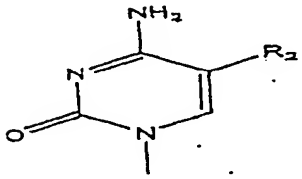
## BRIEF SUMMARY OF THE INVENTION

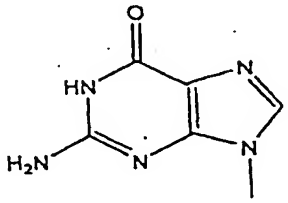
The present invention proposes the use of a compound of the formula I

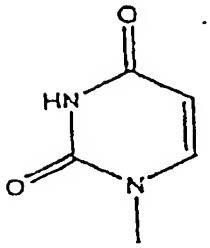


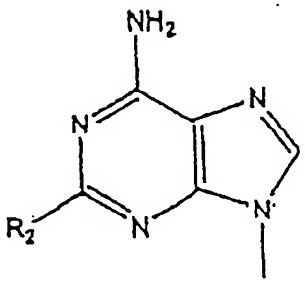
(I)

wherein $R_1$ is a base defined by one of the formulas









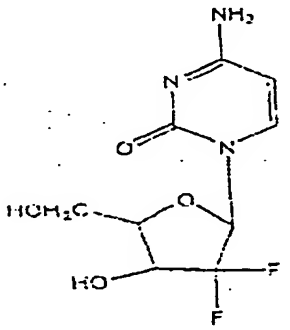
and $R_2$ is hydrogen, $C_1$-$C_4$ alkyl, bromine, fluorine, chlorine, or iodine, or a pharmaceutically acceptable salt thereof, to produce a pharmaceutical for use in immunosuppressive therapy in humans or animals.

The present invention further focuses on the use of a compound of the formula I to produce a pharmaceutical for use in treating autoimmune illnesses in humans and animals.

The present invention also proposes the use of a compound of the formula I to produce a pharmaceutical to use in suppressing the rejection of transplants in humans and animals, preferably to suppress the rejection of bone marrow transplants, heart transplants, corneal transplants small intestine transplants, liver transplants, lung transplants, pancreas transplants, kidney transplants, and skin grafts.

In a further aspect of the invention, the compound of the formula I is used to produce a pharmaceutical for use in treating some illnesses or conditions, selected from: rosacea, acrodermatitis continua, actinic reticuloid, AIDS, alopecia, Alport Syndrome, amyotrophic lateral sclerosis, aphthous stomatitis, pure red cell aplasia, aplastic anemia, asthma, atopic dermatitis, autoimmune enteropathy, Behcet Syndrome, bullous erythema multiforme exudativum, bullous pemphigoid, biliary cirrhosis, corneal melting syndrome, Crohn's Disease, dermatitis herpetiformis, dermatomyositis, diabetes mellitus, Duchenne dystrophy, eczema, epidermolysis bullosa, erythema nodosum leprosum, familial hemophagocytic lymphohistiocytosis, Felty Syndrome, granuloma annulare, Graves ophthalmopathy, hemolytic anemia, hemophilia, hepatitis, ichthyosis, inflammatory bowel disease, interstitial cystitis, interstitial lung disease, keratoconjunctivitis, histiocytosis of the Langerhans' cells, T-cell leukemia, B-cell leukemia, lymphoma, lichen planus, macrophage activation syndrome, Mooren ulcus, morphea, multiple sclerosis, myasthenia gravis, nephropathy, nephrotic syndrome, pustulosis palmaris et plantaris, pemphigus, persistent photosensitivity, pityriasis rubra pilaris, polymyositis, psoriasis, psoriatic arthritis, pulmonary fibrosis, pyoderma gangrenosum, reticular erythematosis, rheumatoid arthritis, sarcoidosis, scleritis, sclerodermia, serpiginous choroiditis, Sjogren Syndrome, sprue, Sweet Syndrome, systemic lupus erythematosus, systemic sclerosis, thrombocytopenia, epidermolysis acuta toxica, colitis ulcerosa, iridocyclochoroiditis, Christian-Weber Disease, drug-induced Christian-Weber panniculitis, Wegener-Klinger granulomatosis.

Preferably, 2'-desoxy-2',2'-difluorocytidine of the formula II




(II)

or a pharmaceutically acceptable salt thereof is used as the compound for the above applications. Preferably, the pharmaceutically acceptable salt that is used is the hydrochloride.

The present invention also focuses on the use of Gemcitabine hydrochloride in combination with one or more of Cyclosporin A, Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s).

Pharmaceutical compositions in unit dose form, which comprise between 1 and 10 mg Gemcitabine hydrochloride and a pharmaceutically acceptable carrier, an extender, or a suitable vehicle, are presented as a further aspect of the invention.

The present invention provides additional pharmaceutical compositions, which comprise a compound of the formula I or a pharmaceutically acceptable salt thereof, one or more of Cyclosporin A, Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s), and a pharmaceutically applicable carrier, an extender, or a suitable vehicle.

Pharmaceutical products that contain a compound of the formula I or a pharmaceutically acceptable salt thereof and one or more of Cyclosporin A, Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s) in combination, and are intended for simultaneous, separate, or subsequent use in treating humans or animals are provided as a further aspect of the present invention.

Preferably, 2'-desoxy-2',2'-difluorocytidine of the formula II or a pharmaceutically acceptable salt thereof is used as a compound in the pharmaceutical compositions and pharmaceutical products of the present invention. Preferably, the pharmaceutically acceptable salt used is the hydrochloride.

## DETAILED DESCRIPTION OF THE INVENTION

The compounds of the formula I (2',2'-difluoronucleosides) used in the present invention are preferably produced by converting a D-glyceraldehyde ketonide with a $C_1$-$C_4$ alkylbromo difluoroacetate to form an alkyl-3-dioxolanyl-2,2-difluoro-3-hydroxypropionate. The hydroxypropionate is then hydrolyzed to form a lactone, which is protected and reduced, to yield a 2-desoxy-2,2-difluororibose or –xylose derivative. The hydroxyl group of this compound is equipped with a leaving group, and the resulting carbohydrate is coupled with a suitable base. The resulting protected nucleoside is finally deprotected in order to provide a compound for use in accordance with the present invention. Details of a method for producing such compounds for use in accordance with the present invention are described in US Patent 5,464,826, which is referenced herein.

Cyclosporin A., Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and corticosteroids are commercially available.

The pharmaceutical compositions and products of the present invention are pharmaceutical formulations that comprise the active ingredient (compound of the formula I) and a pharmaceutical carrier, extender, or vehicle for said ingredient. The formulation of the compositions and products is conventional, and adheres to the customary practices of pharmaceutical chemists.

The active ingredient is contained in the formulation in a ratio of 1 % by weight to 90 % by weight. The active ingredient is usually mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a capsule, a sachet, a paper, or some other container. If the carrier serves as an extender, it may be a solid, semi-solid, or liquid material, which serves as a vehicle, carrier, or medium for the active ingredient. The compositions and products can thus be presented in the form of tablets, pills, powders, pastilles, sachets, capsules, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as solid particles or in a liquid medium), ointments, which may contain up to 10% by weight of the active ingredient, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packed powders.

A number of examples of suitable carriers, vehicles, and extenders are lactose, dextrose, sucrose, sorbitol, mannitol, starches, Arabica gum, calcium phosphate, alginate, tragacanth gum, gelatins, calcium silicate,

microcrystalline cellulose, polyvinyl-pyrrolidone, cellulose, water, syrup, methylcellulose, methyl- and propylhydroxy benzoates, talc, magnesium stearate, and mineral oil. The formulations may also contain lubricants, wetting agents, emulsifying and suspending agents, preservatives, sweeteners, or flavorings. The compositions and products specified in the invention can be formulated using known methods such that they provide a rapid or delayed release of the active ingredient following its administration to the patient or the animal.

The compositions and products are preferably formulated in a unit dose form, wherein each dose contains between approximately 0.1 and approximately 100 mg of the active ingredient. The term "unit dose form" refers to physically separate units, which are designed as unit doses for humans and other mammals, wherein each unit contains a predetermined quantity of active ingredient, which is calculated to produce the desired therapeutic effect, in combination with a suitable pharmaceutical carrier.

If the active ingredient is Gemcitabine hydrochloride, the unit dose will preferably range from approximately 0.5 to approximately 25 mg, and more preferably from approximately 1 mg to approximately 15 mg. It is especially preferable for the unit dose of Gemcitabine hydrochloride to range from approximately 1 to approximately 10 mg, and most preferably from approximately 2 mg to approximately 5 mg.

The following formulation examples represent specific pharmaceutical formulations, in which, in some cases, Gemcitabine hydrochloride is used as the active ingredient. For the formulations, each compound of the formula I may be used as the active ingredient. The examples are intended only as illustrations, and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are produced using the following constituents, wherein "active ingredient" is a compound of the formula I:

| | Quantity (mg/capsule) |
|---|---|
| Active ingredient | 25 |
| Dried starch | 425 |
| Magnesium stearate | 10 |

The constituents listed above are mixed and filled into hard gelatin capsules in quantities of 460 mg.

Formulation 2

A tablet formulation is produced using the constituents listed below:

| | Quantity (mg/capsule) |
|---|---|
| Active ingredient | 2 |
| Microcrystalline cellulose | 500 |
| Silicon dioxide (fumed off) | 10 |
| Stearic acid | 8 |

The constituents are mixed and pressed, forming tablets that weigh 520 mg each.

Formulation 3

An aerosol solution is produced, which contains the following constituents:

| | % by Weight |
|---|---|
| Active ingredient | 0.10 |
| Ethanol | 29.90 |
| Aerosol propellant 22 (chlorodifluoromethane) | 70.00 |

The active ingredient is mixed with ethanol, and the mixture is added to a part of the aerosol propellant 22, cooled to –30° C, and transferred to a filling device. The necessary quantity is then placed in a high-grade steel container, and diluted with the remainder of the aerosol propellant. The valve units are then mounted on the container.

Formulation 4

Tablets, each containing 5 mg active ingredient, are composed as follows:

| | | |
|---|---|---|
| Active ingredient | 5 | mg |
| Starch | 75 | mg |
| Microcrystalline cellulose | 58 | mg |
| Polyvinyl pyrrolidone (as a 10 % solution in water) | 5 | mg |
| Sodium carboxymethyl starch | 5.5 | mg |
| Magnesium stearate | 0.5 | mg |
| Talc | 1 | mg |

The active ingredients, starches, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The polyvinyl pyrrolidone solution is mixed with the resulting powders, which are then passed through a No. 14 mesh U.S. sieve. The granules produced in this manner are dried at 50°-60° C, and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starches, magnesium stearate, and talc are passed through a No. 60 mesh U.S. sieve and are then added to the granules, which, after mixing, are then pressed in a tablet machine, forming tablets that weigh 150 mg each.

Formulation 5

Capsules, each containing 0.5 mg active ingredient, are produced as follows:

| | | |
|---|---|---|
| Active ingredient | 0.5 | mg |
| Starch | 98.5 | mg |
| Microcrystalline cellulose | 98.5 | mg |
| Magnesium stearate | 2.5 | mg |

The active ingredient, cellulose, starch, and magnesium stearate are mixed together, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in quantities of 200 mg.

Formulation 6

Suppositories, each containing 0.1 mg active ingredient, are produced as follows:

| | | |
|---|---|---|
| Active ingredient | 0.1 | mg |
| Glyceride saturated fatty acids, up to | 2 | g |

The active ingredient is passed through a No. 60 mesh U.S. sieve, and suspended in the fatty acids, which have been saturated beforehand using glycerides that were melted using the minimum heat necessary. The mixture is then poured into a suppository form having a nominal capacity of 2 g, and allowed to cool.

Formulation 7

Suspensions, each containing 10 mg of active ingredient per 5-ml dose, are produced as follows:

| | | |
|---|---|---|
| Active ingredient | 10 | mg |
| Sodium carboxymethyl cellulose | 50 | mg |
| Syrup | 1.25 | ml |
| Benzoic acid solution | 0.10 | ml |
| Flavoring | q.v. | |
| Coloring | q.v. | |
| Purified water, up to | 5 | ml |

The active ingredient is passed through a No. 45 mesh U.S. sieve, and mixed with the sodium carboxymethyl cellulose and syrup, forming a smooth paste. The benzoic acid solution, flavoring, and coloring are diluted with a portion of the water, and added under stirring. Sufficient water is then added to achieve the necessary volume.

Intravenous formulations are produced as follows:

Formulation 8

| | | |
|---|---|---|
| Gemcitabine-HCl | 0.1 | mg |
| Isotonic sodium chloride solution | 1000 | ml |

Formulation 9

| | | |
|---|---|---|
| Gemcitabine-HCl | 0.5 | mg |
| Isotonic sodium chloride solution | 1000 | mg |

Formulation 10

| | | |
|---|---|---|
| Gemcitabine-HCl | 1.0 | mg |
| Isotonic sodium chloride solution | 1000 | ml |

Formulation 11

| | | |
|---|---|---|
| Gemcitabine-HCl | 5 | mg |
| Isotonic sodium chloride solution | 1000 | ml |

| | | |
|---|---|---|
| Formulation 12 | | |
| Gemcitabine-HCl | 10 | mg |
| Isotonic sodium chloride solution | 1000 | ml |
| Formulation 13 | | |
| Gemcitabine-HCl | 15 | mg |
| Isotonic sodium chloride solution | 1000 | ml |
| Formulation 14 | | |
| Gemcitabine-HCl | 25 | mg |
| Isotonic sodium chloride solution | 1000 | ml |

The solution of the above listed constituents is administered intravenously, at a rate of 1 ml/minute, for example.

The compositions and products of the invention can be administered to humans or animals in different ways, including orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly, or intranasally. If the active ingredient is Gemcitabine hydrochloride, it is preferably administered via the intravenous pathway.

Daily dosages normally lie within a range of approximately 0.01 to approximately 10 mg/kg body weight (BW) – as a single dose or in separate doses. Preferably, the daily doses range from approximately 0.025 to approximately 5 mg/kg, and most preferably from approximately 0.05 to 0.25 mg/kg. It is understood, however, that the actual quantity of a compound to be administered shall be determined by a physician in light of relevant contributing factors, including the condition to be treated, the specific compound to be administered, the selected mode of administration, the age, weight and responsiveness of the individual patient, and the severity of the patient's symptoms, hence the above-listed dosage ranges shall not serve to limit the scope of the invention in any way.

The immunosuppressive effect of a representative compound of the formula I, 2'-desoxy-2',2'-difluorocytidine (Gemcitabine, dFdC) was demonstrated in the in-vitro and in-vivo tests described below. The use of dFdC represents only a preferred embodiment of the invention; it shall not serve to limit the scope of the invention in any way, and is not intended as such.

dFdC is a pyrimidine antimetabolite with antineoplastic activity against a large number of more solid tumors, including metastasized pancreatic carcinomas, non-parvicellular bronchial carcinomas, ovarian and mammary carcinomas (Kaye, *J. Clin. Oncol* 12, 1527 (1994)). It is a desoxycytidine analogue, which, upon entering the cell, is gradually phosphorylated via desoxycytidine kinase to the corresponding di- and triphosphate as the final product (Plunkett, et al., *Nucleosides Nucleotides* 8, 775 (1989)). The primary mechanism is assumed to be the incorporation of the dFdC triphosphate in DNA, as it effects the inhibition of the synthesis of DNA and cell death.

A number of phase I studies were conducted using dFdC as the antitumor agent, and the greatest success was achieved with phase II studies that involved a weekly administration of the drug (Kaye, *J. Clin. Oncol.* 12, 1527 (1994)). With this scheme of treatment, dFdC is administered intravenously once a week for three weeks, over a period of 30 minutes, followed by a one-week break. It is reported that this mode of administration elicits bone marrow suppression with severe infections (WHO Degree III/IV) in less than 1% of patients. Even after repeated doses of dFdC, no significant reduction in CD4+ and CD8+ lymphocyte subgroups, i.e., no significant immunosuppression was found (Dalkeler, et al., *Anti-Cancer Drugs* 8, 643 (1997)). In contrast, treatment of low-malignant lymphomas with a purine analogue, such as 2-chlorodesoxyadenosine (Cladribin, 2-CdA), in a (daily x 5) scheme is associated with a strong suppression of the CD4+ lymphocytes for more than 12 months (Seymour, et al., *Blood* 83, 2906 (1994)).

Phase I studies, in which dFdC was tested using a (daily x 5) scheme, with a dosage level of 9 $mg/m^2$, effected a significant degree of non-hematological toxicity, including sporadic fever and severe hypertension (O'Rourke, et al. *Eur. J. Cancer* 30A, 417 (1994)). Based upon these results, this scheme was not recommended for further evaluation. Measurements of the intracellular dFdC accumulation following daily administration of low doses and their effect on immunocompetent cells have not yet been conducted.

For the purpose of the present invention, the immunosuppressive effect of dFdC was evaluated, by studying the in-vitro effect of dFdC on lymphocytes, using the lymphocyte colony growth test, and the effect of dFdC in a rat heart transplant model.

- Effect of dFdC on the Colony Formation of T-Lymphocytes

dFdC is available commercially. It is known that the interference of pharmaceuticals in the colony-forming ability of active T-lymphocytes is an acceptable instrument for demonstrating lymphocytotoxic effects (Aye, *Blood* 58, 1043 (1981)). For that reason, mononuclear cells from peripheral blood (PBMC) were cultivated with phytohemagglutinin (PHA) and different dFdC concentrations, in the microagar culture system described in Petzer, et al., *Blood* 78, 2583 (1991). The PBMC were suspended in Iscove's medium, which contains 20% fetal calves' serum and 0.3% agar. 250-µl partial quantities of this suspension, which contained 2 x $10^5$ PBMC, were then plated out on tissue culture plates with multiple depressions. The agar was allowed to solidify at room temperature, and was then coated with 250 µl of a medium containing 0.5% PHA and 0.5% 2-mercaptoethanol (1 x $10^{-1}$ mol/l final concentrations). The cultures were incubated at 37° C in a completely moist atmosphere containing 5% $CO_2$, and the colonies were counted using a reverse microscope, following 7 days incubation.

As is shown in Fig. 1, the PHA-induced lymphocyte proliferation was suppressed by dFdC in a dose-dependent manner, with a concentration of 3.25 ± 0.9 nmol/l resulting in a 50% suppression.

- Effects of dFdC in Rat Heart Transplant Model

Inbred, male LEWIS-(LEW) rats and brown-Norway (BN) rats weighing 200-270 g were obtained from the "Central Institute for the Breeding of Experimental Animals", Hanover, Germany. Heterotopic heart transplants were conducted using microsurgical techniques as described by Schmid, et al., *Eur. Surg. Res.* 30, 61 (1998). Postoperatively, all animals were given as much water and standard rat food as they desired.

dFdC was administered subcutaneously, once per day for 50 days in sequence, starting immediately after surgery began. The daily doses (number of animals per group) amounted to 25 (n=6), 50 (n=5), 75 (n=6), 100 (n=6), 125 (n=6), 150 (n=6), 300 (n=6), 600 (n=2), or 6,000 (n=1) µg/kg of body weight (BW). The control group (n=8) received no treatment.

The pulse activity of the heart transplants was determined via daily palpation. If the heart transplants ceased beating, the animals were killed with an overdose of ether and the hearts and all vital organs were removed for histological purposes. Multiple sections of the left ventricle of the transplant and each native organ were fixed with a 4% buffer solution. Samples embedded in paraffin were cut into 5-µm thick

segments and dyed with hematoxylin and eosin. The preparations were evaluated by a pathologist, who was ignorant of the study, and the rejection was classified according to ISHT criteria (Billingham, et al., *J. Heart Transplant* 9, 587 (1990)).

The effects of dFdC in the rat heart transplant model are shown in Table 1. The results are presented as transplant survival times in days for the different dFdC dosage groups and the control group, which received no dFdC.

A dose-dependent leucopenia occurred in all animals of all groups, and was reversible in animals that received less than 150 µg/kg dFdC.

Table 1

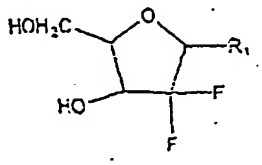
| DFdC Dose (µg/kg/day) | Transplant Survival Time (Days) | Transplant Rejection |
|---|---|---|
| Untreated control animals | 7.1 | Degree IV |
| 25 | 7.3 | Degree IV |
| 50 | 9.2 | Degree IV |
| 75 | 15.7 | Degree IV |
| 100 | 152.8 | Degree IV |
| 125 | 144.2 | Degree IV |
| 150 | 41.5 | None |
| 300 | 16.0 | None |
| 600 | 10.5 | None |
| 6,000 | 4.0 | None |

The results of the above-described study show for the first time a marked immunosuppressive efficacy for dFdC. The transplant survival time was extended in all animals that were administered between 75 and 600 µg/kg body weight of the drug, as compared with untreated control animals. The longest survival time was achieved with 100 to 125 µg/kg body weights. More than 125 µg/kg body weights affected a super-immunosuppression and irreversible bone marrow toxicity.

The effective immunosuppressive dFdC dosage, shown by the above-discussed results, surprisingly is much lower than expected based upon the dosage level of the drug that is necessary for the treatment of malignant diseases.

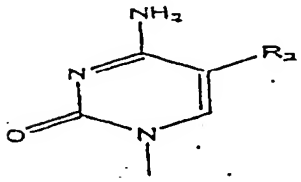
Patent Claims

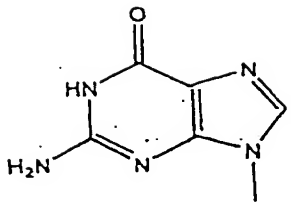
1. Use of a compound of the formula I

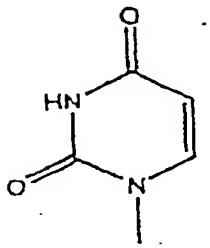


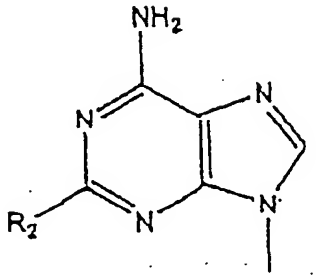
(I)

wherein $R_1$ is a base defined by the formulas









and $R_2$ is hydrogen, $C_1$-$C_4$ alkyl, bromine, fluorine, chlorine or iodine, or a pharmaceutically acceptable salt thereof, for the production of a pharmaceutical for use in immunosuppressive therapy in humans and animals.

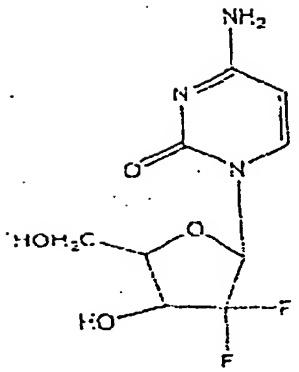
2. Use in accordance with Claim 1 for producing a pharmaceutical for treating autoimmune diseases in humans and animals.

3. The use in accordance with Claim 1 for producing a pharmaceutical for use in suppressing the rejection of transplants in humans and animals.

4. Use in accordance with Claim 1 for producing a pharmaceutical for use in treating an illness or condition, selected from: rosacea, acrodermatitis continua, actinic reticuloid, AIDS, alopecia, Alport Syndrome, amyotrophic lateral sclerosis, aphthous stomatitis, pure red cell aplasia, aplastic anemia, asthma, atopic dermatitis, autoimmune enteropathy, Behcet Syndrome, bullous erythema multiforme exudativum, bullous pemphigoid, biliary cirrhosis, corneal melting syndrome, Crohn's Disease, dermatitis herpetiformis, dermatomyositis, diabetes mellitus, Duchenne dystrophy, eczema, epidermolysis bullosa, erythema nodosum leprosum, familial hemophagocytic lymphohistiocytosis, Felty syndrome, granuloma annulare, Graves ophthalmopathy, hemolytic anemia, hemophilia, hepatitis, ichthyosis, inflammatory bowel disease, interstitial cystitis, interstitial lung disease, keratoconjunctivitis, histiocytosis of the Langerhans' cells, T-cell leukemia, B-cell leukemia, lymphoma, lichen planus, macrophage activation syndrome, Mooren ulcus, morphea, multiple sclerosis, myasthenia gravis, nephropathy, nephrotic syndrome, pustulosis palmaris et plantaris, pemphigus, persistent photosensitivity, pityriasis rubra pilaris, polymyositis, psoriasis, psoriatic arthritis, pulmonary fibrosis, pyoderma gangrenosum, reticular erythematosis, rheumatoid arthritis, sarcoidosis, scleritis, sclerodermia, serpiginous choroiditis, Sjogren Syndrome, sprue, Sweet Syndrome, systemic lupus erythematosus, systemic sclerosis, thrombocytopenia, epidermolysis acuta toxica, colitis ulcerosa, iridocyclochoroiditis, Christian-Weber Disease, drug-induced Christian-Weber panniculitis, Wegener-Klinger granulomatosis.

5. Use in accordance with Claim 3 for suppressing the rejection of bone marrow transplants, heart transplants, corneal transplants, small intestine transplants, liver transplants, lung transplants, pancreas transplants, kidney transplants, and skin grafts.

6. Use in accordance with one or more of Claims 1 through 5, wherein the compound of the formula I is 2'-desoxy-2',2'-difluorocytidine of the formula II



(II)

or a pharmaceutically acceptable salt thereof.

7. Use in accordance with Claim 6, wherein the pharmaceutically acceptable salt is the hydrochloride.

8. Use according to Claim 7, wherein the Gemcitabine hydrochloride is combined with one or more of Cyclosporin A, Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s).

9. Pharmaceutical composition in unit dose form, which comprises between 1 and 10 mg Gemcitabine hydrochloride and a pharmaceutically acceptable carrier, extender, or suitable vehicle.

10. Pharmaceutical composition, which comprises:

- a compound of the formula I named in Claim 1, or a pharmaceutically acceptable salt thereof,
- one or more of Cyclosporin A, Tacrolimus, Mycophenolate Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s), and
- a pharmaceutically acceptable carrier, extender, or vehicle.

11. Pharmaceutical composition in accordance with Claim 10, wherein the compound of the formula I is 2'-desoxy-2',2'-difluorocytidine of the formula II named in Claim 6, or a pharmaceutically acceptable salt thereof.

12. Pharmaceutical composition in accordance with Claim 11, wherein the pharmaceutically acceptable salt is the hydrochloride.

13. Pharmaceutical product, which contains a compound of the formula I named in Claim 1 or a pharmaceutically acceptable salt thereof, and one or more of Cyclosporin A, Tacrolimus, Mycophenolate

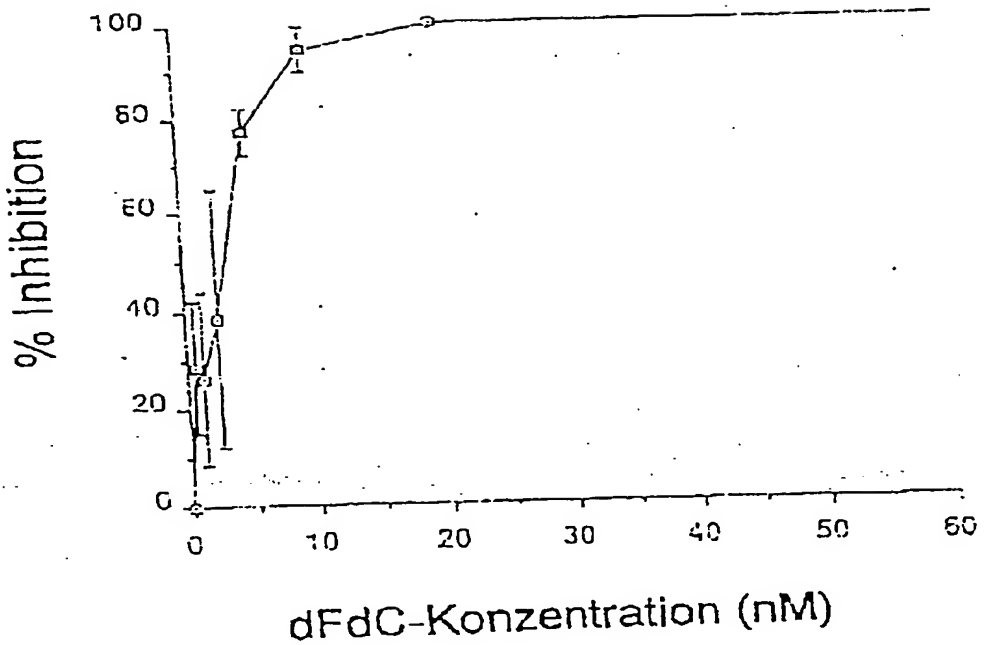
Mofetil, Daclizumab, Rapamycin, and one or more corticosteroid(s) in combination, for the simultaneous, separate, or sequential use in treating the human or animal body.

14. Pharmaceutical product in accordance with Claim 13, wherein the compound of the formula I is 2'-dexosy-2',2'-difluorocytidine of the formula II named in Claim 6, or a pharmaceutically acceptable salt thereof.

15. Pharmaceutical product in accordance with Claim 14, wherein the pharmaceutically acceptable salt is the hydrochloride.

Fig. 1

% Inhibition




dFdC Concentration (nM)